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(21) International Application Number: PCT/EP99/02336 (22) International Filing Date: 26 March 1999 (26.03.99) (30) Priority Data: 98/03851 27 March 1998 (27.03.98) FR (71) Applicants (for all designated States except US): PARKE-DAVIS [FR/FR]; 10, avenue de l'Arche, F-92400 Courbevoie (FR). JULIEN-LAROSE, Christine [FR/FR]; 17, rue Ambroise Paré, F-92700 Colombes (FR). (72) Inventors; and (75) Inventors/Applicants (for US only): JACOBELLI, Henry [FR/FR]; 65, avenue du Général de Gaulle, F-91550 Paray-Vieille-Poste (FR). MARC, Sylvie [FR/FR]; 44, allée des Fours-Blancs, F-91190 Gif-Sur-Yvette (FR). (74) Agents: DURNING, Bernard et al.; Parke-Davis, 3 à 9, rue de la Loge, Boîte postale 100, F-94265 Fresnes Cedex (FR).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHOSPHODIESTERASE IV-INHIBITING DIAZEPINOINDOLES (57) Abstract Metabolites of the products of formula (I) in which A and R are as defined in the description, which are phosphodiesterase 4 inhibitors. <div data-bbox="824 1157 1365 1446"><chem>Rc1ccc2c(c1)c3ccccc3n2C(=O)N(C(=O)Nc4ccccc4)C(=O)A</chem></div> <div data-bbox="1321 1255 1365 1289">(I)</div>		

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Phosphodiesterase IV-inhibiting
diazepinoindoles

Field of the invention

5

The present invention relates to [1,4]diazepino-[6,7,1-*hi*]indoles, and to those for the preparation of medicaments that enable treatment of affections which are amenable to therapy by a phosphodiesterase IV inhibitor.

10 These medicaments are useful, in particular, as anti-inflammatories, anti-allergics, bronchodilators or anti-asthmatics and are devoid of digestive or cardiac side-effects.

15 Technological background of the invention

WO-A-9611690 describes [1,4]diazepino[6,7,1-*hi*]indoles, including in particular (3R)-N-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-*hi*]indol-

20 3-yl)isonicotinamide. (which will be abbreviated to MPTDI in the text which follows).

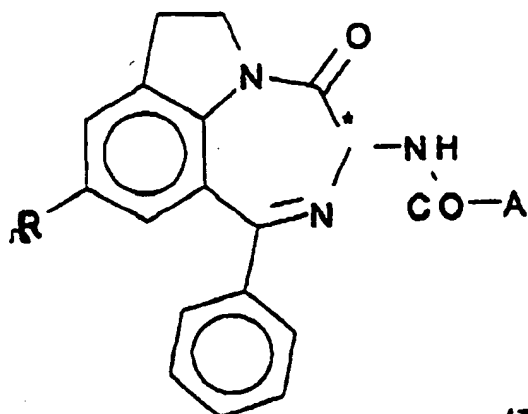
Summary of the invention

25 The subject of the invention is metabolites of the products of formula I and of the products of formula II or III below.

Detailed description of the invention

30 In a first aspect, the invention relates to the metabolites of the products of formula (I):

- 2 -



(I)

in which:

- R is a lower alkyl or alkoxy;
- 5 - A is aryl, nitrogen-containing heteroaryl or sulphur-containing heteroaryl, each optionally substituted with one to three groups independently chosen from halogen, lower alkyl, haloalkyl, lower alkoxy, hydroxyl, acetoxy, amino, t-butoxycarbonylamino, cycloalkylcarbonylamino or acetamido;
- 10 of their racemic forms, of their isomers having a configuration which is determined by the carbon at the 3-position of the diazepinoindol-4-one ring, and of their pharmacologically acceptable salts.
- 15 Preferably, R is a methyl group.

Preferably, the asymmetric carbon has the R configuration.

- 20 Preferably, the product of formula I is the product N-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide, advantageously the configuration is 3R.

- 25 This term «metabolite» covers these products derived from biodegradation by a mammal, in particular humans, of the said products of formula I.

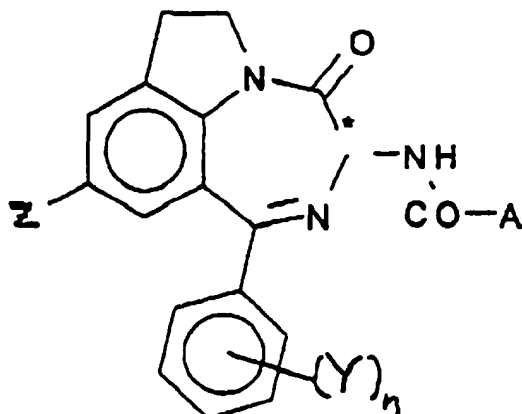
- 3 -

The preferred metabolites are those which are oxidized and/or hydroxylated, on the substituents and/or the rings and/or heterocycles.

- 5 In particular, the invention relates to the metabolites corresponding to the derivatives which are hydroxylated on the pyrrolidine or 1-phenylbenzodiazepine ring.

Advantageously, the products are those in which A is
10 pyridyl, optionally N-oxidized.

In a second aspect, the invention relates to the diazepinoindoles of formula (II)



15

in which:

- Z is a lower alkyl or alkoxy;
- A is aryl, nitrogen-containing heteroaryl or sulphur-
20 containing heteroaryl, each optionally substituted with one to three groups independently chosen from halogen, lower alkyl, haloalkyl, lower alkoxy, hydroxyl, acetoxy, amino, t-butoxycarbonylamino, cycloalkylcarbonylamino or acetamido, the N-oxide or S-oxide forms;
- 25 - Y is hydroxyl or lower alkoxy;
- n is 1 or 2.

of their racemic forms, of their isomers having a configuration which is determined by the carbon at the

3-position of the diazepinoindol-4-one ring, and of their pharmacologically acceptable salts.

Preferably, Y is hydroxyl or methoxy.

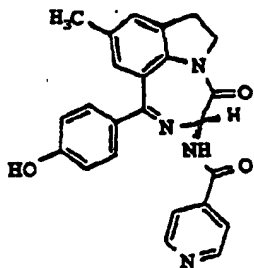
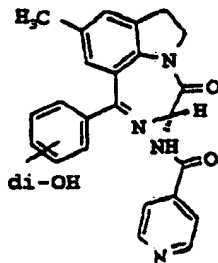
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The phenyl is preferably substituted at the para-position, advantageously with a hydroxyl.

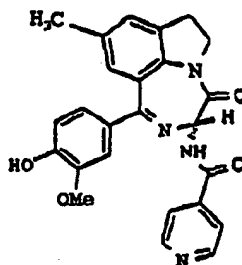
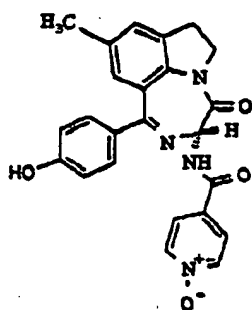
Advantageously, the products are those in which A is
10 pyridyl, optionally N-oxidized.

Among the diazepinoindoles of formula (II), those in which
the asymmetric carbon atom at the alpha-position with
respect to the carbonyl of the diazepine ring has the
15 absolute configuration (R), are preferred.

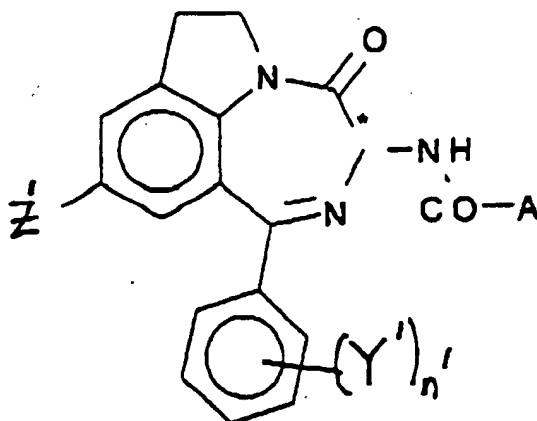
Examples of such products are reproduced below:



20



In a third aspect, the invention relates to the diazepinoindoles of formula (III)



5

in which:

- Z' is hydroxymethyl, formyl, carboxylic acid in its free form, salified, esterified or amidated, hydroxymethyl whose hydroxyl group is esterified;
- 10 - A' is aryl, nitrogen-containing heteroaryl or sulphur-containing heteroaryl, each optionally substituted with one to three groups independently chosen from halogen, lower alkyl, haloalkyl, lower alkoxy, hydroxyl, acetoxy, amino, t-butoxycarbonylamino, cycloalkylcarbonylamino or acetamido,
- 15 the N-oxide or S-oxide forms;
- Y' is hydroxyl or lower alkoxy;
- n' is 0, 1 or 2.

of their racemic forms, of their isomers having a configuration which is determined by the carbon at the
20 3-position of the diazepinoindol-4-one ring, and of their pharmacologically acceptable salts.

Preferably, Z' is chosen from the group consisting of hydroxymethyl; formyl; COOH; CONH₂, COOD where D is a lower alkyl, optionally hydroxylated; -C-O-C(O)-E where E is a lower alkyl, an aryl, cycloalkyl, pyridyl.

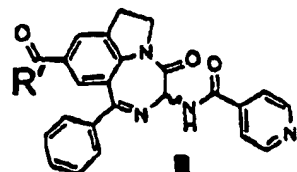
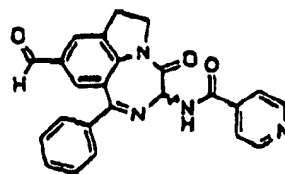
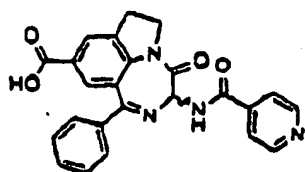
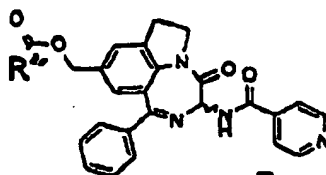
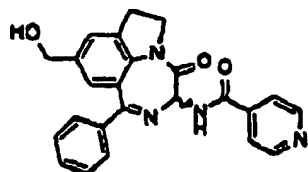
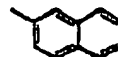
Preferably, Y' is hydroxyl or methoxy.

The phenyl is preferably substituted at the para-position, advantageously with a hydroxyl.

Among the diazepinoindoles of formula (III), those in which the asymmetric carbon atom at the alpha-position with respect to the carbonyl of the diazepine ring has the absolute configuration (R), are preferred.

Advantageously, the products are those in which A' is pyridyl, optionally N-oxidized.

Examples of such products are reproduced below:

 $R' = \text{NH}_2$ $R' = -\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$ **ESTERS** $R'' =$ $-\text{CH}_3$ 

In the foregoing as well as hereinafter:

- aryl is understood to mean a phenyl or naphthyl group;
- nitrogen- or sulphur-containing heteroaryl is understood to mean an unsaturated monocyclic or polycyclic group containing at least one nitrogen or sulphur atom, respectively, and preferably these heterocycles may be four- to seven-membered heteromonocyclic groups containing from 1 to 4 heteroatoms, or unsaturated fused heterocyclic groups containing from 1 to 4 heteroatom; the heteroaryl group may be methylated or ethylated on a positively charged nitrogen;
- halogen is understood to mean fluorine, chlorine, bromine or iodine;
- lower alkyl is understood to mean linear or branched alkyl groups containing from one to four carbon atoms;
- cycloalkyl is understood to mean cyclopropyl, cyclobutyl and cyclopentyl groups;
- lower alkoxy is understood to mean an O-alkyl group in which the alkyl group is a lower alkyl as defined above;
- haloalkyl is understood to mean a mono-, di- or trihaloalkyl containing from 1 to 4 carbon atoms.

A review of salts which are acceptable in pharmacy will be found in J. Pharm. Sci., 1977, 66, 1-19. However, pharmacologically acceptable salt of a compound of formula (I) possessing a basic portion is understood to mean the addition salts of the compounds of formula (I) which are formed from nontoxic inorganic or organic acids such as, for example, the salts of hydrobromic, hydrochloric, sulphuric, sulphamic, phosphoric, nitric, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, mucic, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulphanilic, acetoxymaleic, fumaric, toluenesulphonic, ethanedisulphonic, oxalic, isethionic and the like, acids. The various quaternary ammonium salts of the derivatives (I) are also included in this category of the compounds of the invention. And

pharmacologically acceptable salt of a compound of formula (I) possessing an acidic portion is understood to mean the commonplace salts of the compounds of formula (I) which are formed from nontoxic inorganic or organic bases
5 such as, for example, alkali metal and alkaline-earth metal hydroxides (lithium, sodium, potassium, magnesium and calcium hydroxides), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or alternatively quaternary ammonium hydroxides such
10 as tetramethylammonium hydroxide.

The invention also relates to the above products as a medicament, and in particular for combating inflammatory diseases, allergic diseases and bronchoconstriction, or
15 which is useful in the treatment of asthma, characterized in that it comprises a diazepinoindole according to the invention, in a pharmaceutical dosage form which is suited to the disease to be treated. The invention also relates to the use of the above products for the preparation of the
20 above-mentioned medicaments.

The compounds according to the invention may be synthesized by conventional routes from compounds of formula I as described in Application WO-A-9611690, by biological routes
25 or by chemical synthesis.

The following examples illustrate the use of the products of the invention without however limiting it.

30 Experimental part

Metabolism in vitro of MPTDI in humans

The profile and the identification of the metabolites of MPTDI were obtained after incubation of the product with
35 human hepatic microsomes. The results were compared with those obtained on rat hepatic microsomes. The metabolic

profiles obtained by HPLC coupled to a mass spectrometer in these two species are represented in Figure 1. In some cases, the mass spectra obtained were compared with those of reference substances synthesized by the chemical route. It is deduced therefrom that the profiles obtained on human and rat microsomes are similar: Table 1 collates the measured proportions of the metabolites for these two species.

Table 1: Proportions (%) of the metabolites obtained on human and rat hépatic microsomes

<u>Compound</u>	<u>Human microsomes</u>	<u>Rat microsomes</u>
MPTDI	79	38.2
OH on 9-CH ₃	4.2	24.3
OH on pyrrolidine	7.4	13
OH on Bdz*	7.1	2.6
N-oxide	0.7	5.1
Other	1.2	traces

Bdz means 1-phenylbenzodiazepine ring

Examples of synthesis of the compounds.

Stage No. 1: N-(9-cyano-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide

30 ml of water, 7 ml of concentrated hydrochloric acid and 10 g (25.2 mmol) of N-(9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-hi]indol-3-yl)-isonicotinamide are successively introduced into a 250-ml three-necked flask. The orange-red solution obtained is cooled to 0°C. A solution of sodium nitrite (1.83 g, 26.5 mmol) in 5 ml of water is poured therein at a temperature of less than 5°C. The orange-yellow solution is

kept stirring for 30 min at 0°C. The reaction mixture is neutralized with about 3 g of Na₂CO₃, while maintaining a temperature of less than 5°C; foams are formed during the neutralization. The liquors are transferred rapidly into a three-necked flask, with stirring, containing a solution of NaC≡N (3.04 g, 62.0 mmol) and of CuC≡N (2.72 g, 30.4 mmol) in 10 ml of water, while maintaining the temperature at 0°C. Foams appear; a few millimetres of ice-cold water are added. The reaction medium is stirred for 30 min at about 0°C and then extracted with twice 200 ml of CH₂Cl₂. The medium is filtered on infusorial earth and the phases are separated after settling out. The organic phase is washed with twice 200 ml of water and then dried over anhydrous Na₂SO₄. The solvent is removed under vacuum. The brown foamy residue is purified by rapid chromatography on a silica column, eluting with CH₂Cl₂ progressively enriched with MeOH. 5.6 g (13.7 mmol) of product are obtained in the form of a yellow powder.

Yield = 54.5% - m.p. = 174°C Analysis conforms for C₂₄H₁₇O₂N₅ (0.3 H₂O)

TLC (CH₂Cl₂/MeOH 95/5 v/v): R_f = 0.70.

¹H NMR δ (ppm): 3.15-3.25 (m, 1H); 3.35-3.50 (m, 1H); 4.05 (q, 1H); 4.5 (td, 1H); 5.55 (d, 1H); 7.4-7.6 (m, 5H); 7.7 (s, 1H); 7.95 (d, 2H); 8.0 (s, 1H); 8.75 (d, 2H); 10.05 (d, 1H).

IR: 3300, 2200, 1690, 1660, 1610, 1510, 1430, 1280, 1130, 890, 850, 700 cm⁻¹

Stage No. 2: N-(9-aminomethyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide

A solution of the nitrile obtained in stage No. 1 (5.6 g, 13.7 mmol) in 280 ml of MeOH is introduced into a 500-ml stainless steel autoclave. The apparatus is cooled with a dry ice/acetone bath at about -40°C. 35 ml of liquid ammonia are then added. In parallel, Raney nickel, washed three

times with water, is carefully introduced into the reactor, followed by methanol. After hermetically closing the apparatus, it is purged three times with nitrogen and then with hydrogen. The autoclave is placed under a hydrogen
5 pressure of 4 bar and stirred. The internal temperature is raised to 50-55°C for 3 h. After cooling, the apparatus is purged under vacuum and under nitrogen. The catalyst is removed by filtration on infusorial earth and washed with MeOH. The filtrate is evaporated under vacuum. A foamy
10 residue of 5.3 g is obtained and purified by rapid chromatography, eluting with CH₂Cl₂ progressively enriched with methanol containing 10% ammonium hydroxide. 2.4 g (5.8 mmol) of a beige powder are obtained. Yield = 42%

15 The product is analysed in the form of a dihydrochloride prepared with an approximately 3.5 N hydrochloric ether and crystallized from an isopropanol/ methanol mixture.

m.p. > 270°C - Analysis conforms for C₂₄H₂₁N₅O₂.2HCl (0.5 H₂O)
TLC (CH₂Cl₂/MeOH containing 10% NH₄OH 90/10 v/v): R_f = 0.50.

20 ¹H NMR (base) δ (ppm): 1.80 (m, 2H); 3-3.1 (m, 1H); 3.2-3.3 (m, 1H); 3.8 (s, 2H); 3.9-4.00 (m, 1H); 4.6-7.7 (m, 1H); 5.5 (d, 1H); 7.1 (s, 1H); 7.3-7.5 (m, 6H); 7.7 (d, 2H); 8.1 (d, 1H); 8.7 (d, 2H).

IR (di-HCl): 3300, 2800, 2600, 1680, 1650, 1600, 1540, 1440,
25 1280, 1230, 1100, 1000, 830, 760, 700 cm⁻¹

Stage No. 3: N-(9-hydroxymethyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide

30 2.4 g (5.8 mmol) of the product obtained in stage No. 2 dissolved in 21.2 ml of 10% acetic acid (w/v) are cooled to 0°C with a brine bath; a solution of sodium nitrite (1.25 g, 18 mmol) in 7 ml of water is slowly added. The mixture is stirred for 2 h at 0°C. After alkalinizing with 14 ml of 4 N
35 sodium hydroxide, it is extracted with twice 50 ml of CH₂Cl₂. The organic phase is dried over Na₂SO₄ and then evaporated

under vacuum. The residue obtained is purified by rapid chromatography, eluting with CH_2Cl_2 progressively enriched with MeOH. The fractions of interest are concentrated under vacuum. The product is crystallized from 18 ml of CH_2Cl_2 . The precipitate is filtered off and then dried under vacuum. 0.9 g is obtained. Yield: 38% - White powder m.p. = 260°C - Analysis conforms for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_3$ (0.1 CH_3OH), (0.1 H_2O) - TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 v/v): $R_f = 0.80$.

^1H NMR δ (ppm): 3.1 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.5 (m, 3H); 5.2 (t, 1H); 5.4 (d, 1H); 7.2 (s, 1H); 7.4-7.6 (m, 6H); 8.0 (d, 2H); 8.80 (d, 2H); 10.0 (d, 1H)
IR: 3400, 3300, 3050, 2850, 1680, 1660, 1530, 1480, 1440, 1400, 1360, 1290, 1220, 1190, 1120, 1060, 900, 860, 780, 760, 700 cm^{-1}

Separation of the optical isomers of N-(9-hydroxymethyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide

This was carried out on a Merck high-performance liquid chromatography system composed of a pump and a UV detector, provided with a fraction collector. The chiral column used is of the Chiralcel OJ type, 20 x 250 mm, 10 μm particles, thermostated at 35°C . The injections are twenty times 5 ml of an ethanolic solution at 7 mg/ml, by means of a Rheodyne valve. The operating conditions are the following: solvent: hexane/ethanol 75/25 (v/v), flow rate: 6ml/min, pressure: 12 bar, UV detection: 254 nm. The fractions containing each isomer are collected and then the solvent removed under vacuum.

1st isomer: retention time = 28-38 min.

Beige crystallized residue, purified by dissolution in a $\text{CH}_2\text{Cl}_2/\text{MeOH}$ mixture, and then precipitation by addition of hexane. 0.190 g of a beige powder is obtained. m.p. = 251°C - Analysis conforms for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_3$ (0.5 CH_3OH) - TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 v/v): $R_f = 0.80$.

Chiral HPLC (Chiralcel OJ column, 250 x 4.6 mm, 10 μ m particles, thermostated at 35°C, solvent: hexane/ethanol 70/30 (v/v), flow rate: 1.2 ml/min, UV detection at 254 nm): retention time = 7.8 min at 100% optical purity.

- 5 ^1H NMR δ (ppm): 3.1 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.5 (m, 3H); 5.2 (t, 1H); 5.4 (d, 1H); 7.2 (s, 1H); 7.4-7.6 (m, 6H); 8.0 (d, 2H); 8.80 (d, 2H); 10.0 (d, 1H)
IR: 3380, 2800, 1690, 1650, 1530, 1425, 1360, 1180, 1120, 1060, 900, 840, 780, 690 cm^{-1}

10

2nd isomer: retention time = 41-54 min.

In the same manner, 0.220 g of a beige powder is obtained. m.p. = 253°C - Analysis conforms for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_3$ (0.5 CH_3OH) TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 v/v): R_f = 0.80.

- 15 Chiral HPLC (Chiralcel OJ column, 250 x 4.6 mm, 10 μ m particles, thermostated at 35°C, solvent: hexane/ethanol 70/30 (v/v), flow rate: 1.2 ml/min, UV detection at 254 nm): retention time = 10.8 min at 99% optical purity.

- ^1H NMR δ (ppm): 3.1 (m, 1H); 3.3 (m, 1H); 3.9 (q, 1H); 4.5 (m, 3H); 5.2 (t, 1H); 5.4 (d, 1H); 7.2 (s, 1H); 7.4-7.6 (m, 6H); 8.0 (d, 2H); 8.80 (d, 2H); 10.0 (d, 1H)
20 IR: 3380, 2800, 1690, 1650, 1530, 1425, 1360, 1180, 1120, 1060, 900, 840, 780, 690 cm^{-1}

- 25 N-(9-formyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)-isonicotinamide

0.100 g (0.24 mmol) of N-(9-hydroxymethyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)-

- 30 isonicotinamide and 20 ml of CH_2Cl_2 are introduced successively into a 50-ml one-necked flask. The mixture is stirred and 0.200 g (0.93 mmol) of pyridinium chlorochromate are added. The suspension is stirred for 1 h at 20-25°C. The purification is carried out directly on the reaction mixture
35 by rapid chromatography on a silica column, eluting with CH_2Cl_2 enriched with MeOH. The residue obtained after removal

of the solvent is concreted in a few millilitres of ether. 0.022 g (0.054 mmol) of a beige powder is obtained. - TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 v/v): R_f = 0.50.

^1H NMR δ (ppm): 3.07-3.18 (m, 1H); 3.2-3.35 (m, 1H); 3.9-4.0 (q, 1H); 4.5-4.6 (t, 1H); 5.50 (d, 1H); 7.2-7.3 (m, 2H); 7.3-7.4 (m, 3H); 7.6 (s, 1H); 7.7 (d, 2H); 7.85 (s, 1H); 8.3 (d, 1H); 8.65 (d, 2H); 9.75 (s, 1H)

4-Oxo-1-phenyl-3[(pyridine-4-carbonyl)amino]-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indole-9-carboxylic acid 2-hydroxyethyl ester

0.6 g (1.5 mmol) of N-(9-cyano-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide is introduced into a three-necked flask followed by 110 ml of ethylene glycol; the mixture is stirred and 1.5 ml (4.5 mmol) of 3 N sodium hydroxide are added. The medium is stirred for 4 days at 20-25°C, is then poured over 400 ml of water and ice, is acidified with 1 N hydrochloric acid and is then extracted with twice 200 ml of CH_2Cl_2 . The organic phases are dried over Na_2SO_4 and the solvent removed by concentrating under vacuum. The residue is purified by rapid chromatography on silica, eluting with CH_2Cl_2 enriched with MeOH. 0.13 g of product is obtained. Yield = 18%. - TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 v/v): R_f = 0.36

^1H NMR δ (ppm): 2.45 (OH); 3.05-3.2 (m, 1H); 3.25-3.4 (m, 1H); 3.85 (t, 2H); 4.0 (q, 1H); 4.35-4.5 (m, 2H); 4.6 (td, 1H); 5.55 (d, 1H); 7.25-7.35 (m, 2H); 7.4-7.5 (m, 3H); 7.75 (d, 2H); 7.9 (s, 1H); 8.0 (s, 1H); 8.1 (d, 1H); 8.7 (d, 2H)

Isonicotinic acid 4-oxo-1-phenyl-3[(pyridine-4-carbonyl)-amino]-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-9-ylmethyl ester

5 0.1 g (0.24 mmol) of N-(9-hydroxymethyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide in 10 ml of anhydrous CH₂Cl₂ is introduced into a three-necked flask under an inert atmosphere and protected from moisture, it is stirred and 0.0475 g (0.27 mmol) of
10 isonicotinoyl chloride hydrochloride is introduced at a temperature close to 15°C. The suspension is stirred for 10 min at this temperature and then heated under reflux for 1.5 h. 10 ml of CH₂Cl₂ are added and the mixture is treated with a dilute NaHCO₃ solution. The organic phase is decanted
15 off and the solvent is removed by concentrating under vacuum. The 0.1 g residue is purified by rapid chromatography on silica, eluting with CH₂Cl₂ enriched with MeOH. 0.028 g of product is obtained. Yield = 22%
TLC (CH₂Cl₂/MeOH 95/5 v/v): R_f = 0.57.

20 ¹H NMR δ (ppm): 3.0-3.2 (d, 2H); 3.3-3.45 (m, 1H); 4.0 (q, 1H); 4.65 (td, 1H); 5.3 (d, 2H); 5.55 (d, 1H); 7.25-7.35 (m, 3H); 7.4-7.55 (m, 4H); 7.7 (d, 2H); 7.75 (d, 2H); 8.0 (d, 1H); 8.7 (d, 2H); 8.75 (d, 2H)

25 **Benzoic acid 4-oxo-1-phenyl-3[(pyridine-4-carbonyl)amino]-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-9-ylmethyl ester**

The title compound is prepared in a similar manner by the
30 above process, but using 10 equivalents of benzoyl chloride and maintaining the reflux for 4.5 h.

After treatment and purification, 0.020 g of product is obtained.

TLC (CH₂Cl₂/MeOH 95/5 v/v): R_f = 0.61.

35 ¹H NMR δ (ppm): 3.05-3.2 (m, 1H); 3.3-3.45 (m, 1H); 4.05 (q, 1H); 4.7 (td, 1H); 5.35 (d, 2H); 5.65 (d, 1H); 7.3-7.5

- 17 -

(m, 6H); 7.5-7.65 (m, 4H); 7.8 (d, 2H); 8.05 (d, 2H);
8.2 (d, 1H); 8.8 (d, 2H)

Cyclohexanecarboxylic acid 4-oxo-1-phenyl-3[(pyridine-4-
5 carbonyl)amino]-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-
hi]indol-9-ylmethyl ester

The title compound is prepared in a similar manner by the
above process, but using 2.3 equivalents of
10 cyclohexanecarboxylic acid chloride and maintaining the
reflux for 2.5 h.

After treatment and purification, 0.020 g of product is
obtained.

TLC (CH₂Cl₂/MeOH 95/5 v/v): R_f = 0.40.

15 ¹H NMR δ (ppm): 1.1-1.9 (m, 10H); 2.15-2.3 (m, 1H); 3.0-3.15
(m, 1H); 3.25-3.4 (m, 1H); 3.95 (q, 1H); 4.6 (td, 1H);
5.0 (d, 2H); 5.55 (d, 1H); 7.15 (s, 1H); 7.25-7.5 (m,
6H); 7.75 (d, 2H); 8.1 (d, 1H); 8.75 (d, 2H).

20 Acetic acid 4-oxo-1-phenyl-3[(pyridine-4-carbonyl)amino]-
3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-9-ylmethyl
ester

The title compound is prepared in a similar manner by the
25 above process, but using 3 equivalents of acetyl chloride
and maintaining the reflux for 3 h. After treatment and
purification, 0.020 g of product is obtained.

TLC (CH₂Cl₂/MeOH 95/5 v/v): R_f = 0.37.

¹H NMR δ (ppm): 2.0 (s, 3H); 3.05-3.15 (m, 1H); 3.25-3.40 (m,
30 1H); 3.95 (q, 1H); 4.6 (td, 1H); 5.0 (d, 2H); 5.5 (d,
1H); 7.2 (s, 1H); 7.25-7.35 (m, 2H); 7.4-7.5 (m, 4H);
7.7 (d, 2H); 8.05 (d, 1H); 8.7 (d, 2H).

2-Naphthyl derivative of the Z group

The title compound, 2-naphthyl ester, is prepared in a similar manner by the above process, but using 2-naphthoyl chloride. After treatment and purification, 0.007 g of product is obtained.

5 TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 v/v): $R_f = 0.48$.

^1H NMR δ (ppm): 3.1-3.3 (m, 1H); 3.35-3.5 (m, 1H); 4.05 (q, 1H); 4.6-4.8 (t, 1H); 5.4 (d, 2H); 5.65 (d, 1H); 7.3-7.4 (m, 2H); 7.4-7.45 (m, 2H); 7.5-7.7 (m, 5H); 7.8 (d, 2H); 7.85-7.9 (m, 2H); 7.95 (d, 1H); 8.05-8.15 (m 2H);
10 8.6 (s, 1H); 8.8 (d, 2H).

N-Oxide derivative of pyridyne.

2.0 g (5 mmol) of MPTDI and 100 ml of CH_2Cl_2 are introduced
15 into a three-necked flask protected from moisture; the solution is stirred and cooled by an ice bath. A solution of 1.9 g (5.5 mmol) of 3-chloroperbenzoic acid in 50 ml of CH_2Cl_2 is poured in over 10 min at a temperature close to 2°C . The medium is kept stirring for 2 h at this
20 temperature. The reaction liquors are washed successively with a solution of Na_2CO_3 and then with a saturated solution of NaCl . After drying over Na_2SO_4 , the solvent is removed by distillation under a vacuum of 20 mm Hg at 50°C . The 2.0 g of residue are purified by rapid chromatography on a silica
25 column, eluting with CH_2Cl_2 progressively enriched with MeOH. 0.7 g of concreted product is obtained in an ether/ethyl acetate mixture. - Beige powder - m.p. = 220°C

TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 v/v): $R_f = 0.35$.

^1H NMR δ (ppm): 2.3 (s, 3H); 3.0-3.1 (m, 1H); 3.2-3.3 (m, 1H); 3.85-3.95 (m, 1H); 4.5-4.6 (m, 1H); 5.45 (d, 1H);
30 6.95 (s, 1H); 7.25 (s, 1H); 7.3-7.5 (m, 5H); 7.75 (d, 2H); 8.2 (m, 3H)

I.R.: 3400, 1660, 1540, 1480, 1430, 1350, 1240, 1180, 1120,
1020, 850, 700 cm^{-1}

Biological part

The compounds according to the invention are biologically active, as demonstrated by the tests below carried out on these compounds.

- Phosphodiesterase-inhibiting activity

The capacity of the compounds of formula (I) of the invention to inhibit cyclic nucleotide phosphodiesterases is evaluated by measuring their IC_{50} (concentration necessary for inhibiting 50% of the enzyme activity). In the case of the PDE IV enzymes, this value is compared with the IC_{50} of rolipram, a specific PDE IV inhibitor, by the ratio of the IC_{50} of rolipram to the IC_{50} of the test product with respect to the same enzyme preparation.

The different types of phosphodiesterases are obtained partially purified on a DEAE-cellulose column from guinea pig trachea and dog aorta according to a method adapted from W.J. Thompson et al., 1979, Advances in Cyclic Nucleotide Research, Vol. 10: 69-92, ed. G. Brooker et al. Raven Press, New York, and from P.J. Silver et al., 1988, Eur. J. Pharmacol. 150: 85-94.

Next, the measurement of the enzymatic activity of different types of PDE, and in particular PDE IV, is carried out according to a method also adapted from W.J. Thompson, *Ibidem*.

To determine the IC_{50} , the enzymatic activity is measured in the presence of the inhibitor within a range of concentrations from 0.1 to 100 μM .

The results show that the products of the invention generally inhibit the PDE IV enzyme of guinea pig trachea

- 20 -

more effectively than rolipram, and in a number of cases are twice to three times as active as rolipram.

Moreover, tests carried out on PDEs of different types, 5 purified from guinea pig trachea or from dog aorta, show that the IC_{50} values obtained with the products of the invention with respect to PDEs of type III and of type I and V are much higher than those measured for the type IV PDEs.

10 These results are evidence of a potent and selective inhibitory activity for the products of the invention with respect to the PDE IV enzymes.

- Anti-inflammatory and anti-allergic activity in vivo

15

The effects of the product of the invention were studied in guinea pigs in a model of eosinophil infiltration induced by an antigenic stimulation or by exposure to a PAF spray according to a methodology described by Lagente V. et al., 20 (1994) Br. J. Pharmacol. 112, 83P.

25

The administration of products of the Examples (1 - 30 mg/kg p.o.) significantly decreases the number of eosinophils in the bronchoalveolar lavage fluid.

The administration of products of the invention also decreases the inflammatory responses induced by intratracheal instillation of IL-5 in guinea pigs.

30 - Inhibition of the secretion of cytokines

The activity of the products of the invention on the secretion of cytokines by human mononuclear cells was measured in vitro according to a method described by Konno 35 S. et al. (1994) Eur. J. Pharmacol. 264: 265-268 and Endo H. et al. (1993) Int. Arch. Allergy Immunol. 101: 425-430 for

the interleukins, and by Semmler J. et al. (1993) Int. J. Immunopharmac. 15: 409-413 and Verghese M.W. et al. (1995) J. Pharmacol. Exp. Ther. 272: 1313-1320 for TNF α .

5 Toxicity is evaluated in rats through per os administration. Administered in aqueous suspension in 1% methylcellulose, at the dose of 100 mg/kg/d, the products according to the invention showed no activity which can be linked to a toxic effect.

10

In particular, the absence of emesis-producing effects is observed.

15 These results demonstrate the anti-inflammatory and/or anti-allergic activity of the products of the invention. Hence the products of the invention will be especially useful for the treatment or prevention of:

- allergic pathologies, and in particular asthma and atopic dermatitis;
- 20 - inflammatory pathologies, in particular those affecting the bronchus, but also rheumatoid arthritis and also inflammatory intestinal complaints (haemorrhagic rectocolitis and Crohn's disease);
- including, where it is present, an autoimmune component.

25

Pharmaceutical formulation part

The products of the invention are administered in the form of compositions suited to the nature and extent of the
30 complaint to be treated. The daily dosage in man is usually between 2 mg and 1 g of product, which can be taken in one or several doses. The compositions are prepared in forms which are compatible with the administration route envisaged, such as, for example, tablets, dragées, capsules,
35 mouthwashes, aerosols, powders for inhalation, suppositories, gels or suspensions. These compositions are

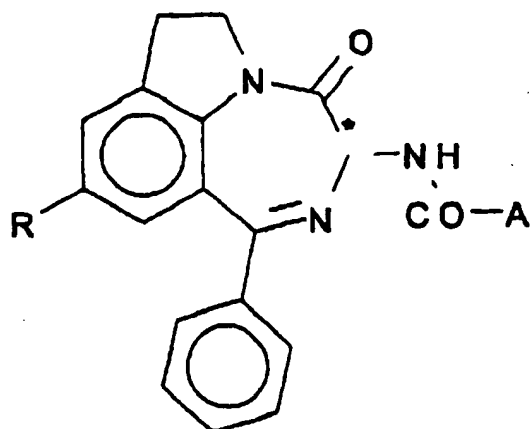
prepared by methods familiar to a person skilled in the art, and comprise from 0.5 to 60% by weight of active principle and 40 to 99.5% by weight of suitable pharmaceutical vehicle which is compatible with the active principle and the physical form of the composition envisaged. The composition and the preparation of tablets containing a compound of the invention are presented by way of example:

	Active substance	
	of formula (I)	1 to 75 mg
10	Lactose	124 to 74 mg
	Microcrystalline	
	cellulose	36 to 60 mg
	Polyvinylpyrrolidone	6 mg
	Sodium carboxymethyl	
15	starch	8 mg
	Magnesium stearate	1 mg

Mix the active substance, lactose, microcrystalline cellulose and carboxymethyl starch. Wet and granulate using an aqueous or alcoholic solution of polyvinylpyrrolidone of appropriate concentration. Dry and calibrate the granulate. Homogeneously mix the magnesium stearate. Tablet on the basis of 200 g per tablet.

Claims

1. Metabolites of the products of formula (I):



(I)

5

in which:

- R is a lower alkyl or alkoxy;
- A is aryl, nitrogen-containing heteroaryl or sulphur-containing heteroaryl, each optionally substituted with one to three groups independently chosen from halogen, lower alkyl, haloalkyl, lower alkoxy, hydroxyl, acetoxy, amino, t-butoxycarbonylamino, cycloalkyl-carbonylamino or acetamido; of their racemic forms, of their isomers having a configuration which is determined by the carbon at the 3-position of the diazepino-indol-4-one ring, and of their pharmacologically acceptable salts.

10

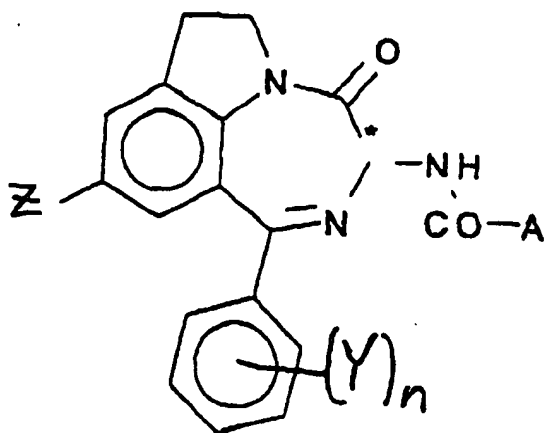
15

- 20 2. Metabolites according to Claim 1, where R is the methyl group in the product of formula I

3. Metabolites according to Claim 1 or 2, of the product N-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide.

25

4. Metabolites according to Claim 1, 2 or 3, where the asymmetric carbon of the product of formula I has the R configuration.
5. Products according to any one of Claims 8 to 11, where A is pyridyl, optionally N-oxidized.
6. Metabolites according to Claim 1, of the product (3R)-N-(9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)isonicotinamide.
7. Metabolites according to any one of Claims 1 to 6, which are oxidized and/or hydroxylated, on the substituents and/or the rings and/or heterocycles.
8. Metabolites according to any one of Claims 1 to 6, corresponding to the derivatives hydroxylated on the pyrrolidine or 1-phenylbenzodiazepine ring.
9. Diazepinoindole products of formula (II)



in which:

- Z is a lower alkyl or alkoxy;
- A is aryl, nitrogen-containing heteroaryl or sulphur-containing heteroaryl, each optionally substituted with one to three groups independently chosen from halogen,

lower alkyl, haloalkyl, lower alkoxy, hydroxyl, acetoxyl, amino, t-butoxycarbonylamino, cyclo-alkylcarbonylamino or acetamido, the N-oxide or S-oxide forms;

5 - Y is hydroxyl or lower alkoxy;

- n is 1 or 2.

of their racemic forms, of their isomers having a configuration which is determined by the carbon at the 3-position of the diazepinoindol-4-one ring, and of
10 their pharmacologically acceptable salts.

10. Products according to Claim 9, where Y is hydroxyl or methoxy.

15 11. Products according to Claim 9 or 10, where the phenyl is substituted at the para-position.

12. Products according to Claim 11, where the phenyl is substituted at the para-position with a hydroxyl.

20

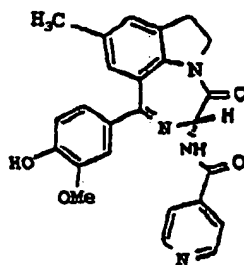
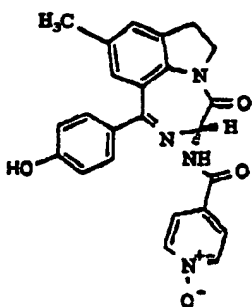
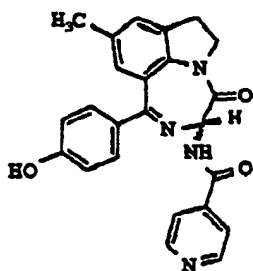
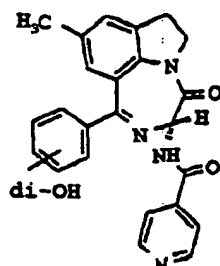
13. Products according to any one of Claims 9 to 12, where A is pyridyl, optionally N-oxidized.

25

14. Products according to any one of Claims 9 to 13, where the asymmetric carbon at the alpha-position in relation to the carbonyl or the diazepine ring has an absolute configuration (R).

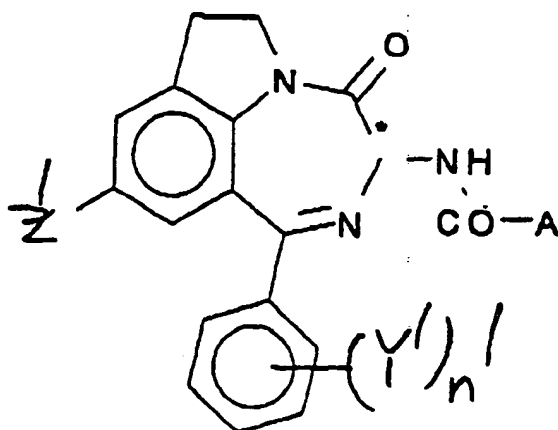
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15. Products according to any one of Claims 9 to 14, chosen from the following products



5

16. Diazepinoindol products of formula (III)



- 27 -

- Z' is hydroxymethyl, formyl, carboxylic acid in its free form, salified, esterified or amidated, hydroxymethyl whose hydroxyl group is esterified;

5 - A' is aryl, nitrogen-containing heteroaryl, or sulphur-containing heteroaryl, each optionally substituted with one to three groups independently chosen from halogen, lower alkyl, haloalkyl, lower alkoxy, hydroxyl, acetoxy, amino, t-butoxycarbonylamino, cycloalkylcarbonylamino or acetamido, the N-oxide or S-oxide
10 forms;

- Y' is hydroxyl or lower alkoxy;

- n' is 0, 1 or 2.

of their racemic forms, of their isomers having a configuration which is determined by the carbon at the
15 3-position of the diazepinoindol-4-one ring, and of their pharmacologically acceptable salts.

17. Products according to Claim 16, where Z' is chosen from the group consisting of hydroxymethyl; formyl; COOH; CONH₂, COOD where D is a lower alkyl, optionally
20 hydroxylated; -C-O-C(O)-E where E is a lower alkyl, an aryl, cycloalkyl, pyridyl.

18. Products according to Claim 16 or 17, where Y' is
25 hydroxyl or methoxy.

19. Products according to any one of Claims 16 to 18, where the phenyl is substituted at the para-position.

30 20. Products according to Claim 19, where the phenyl is substituted at the para-position with a hydroxyl.

21. Products according to any one of Claims 15 to 19, where A' is pyridyl, optionally N-oxidized.

35

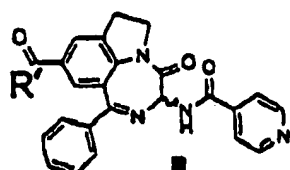
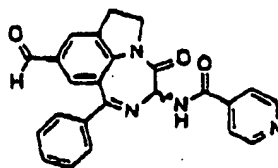
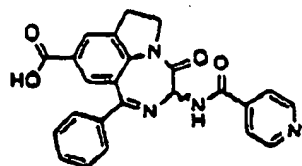
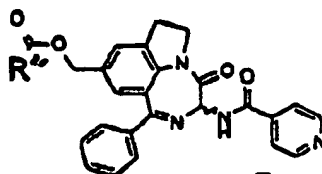
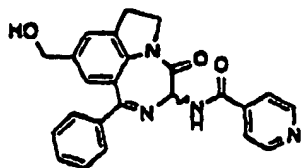
- 28 -

22. Products according to any one of Claims 16 to 21, where the asymmetric carbon atom at the alpha-position with respect to the carbonyl of the diazepine ring has the absolute configuration (R).

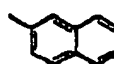
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23. Products according to any one of Claims 16 to 22, chosen from the following products

- 29 -

 $R' = \text{NH}_2$ $R' = -\text{O}-\text{CH}_2-\text{CH}_2-\text{OH}$  $R'' =$

ESTERS

 $-\text{CH}_3$ 

- 30 -

24. Use of a product according to any one of the preceding claims, for preparing a medicament that enables complaints which are amenable to therapy by a phosphodiesterase IV inhibitor to be treated.

5

25. Use according to Claim 24, characterized in that the medicament enables inflammatory pathologies such as asthma or rheumatoid arthritis to be prevented or treated.

10

26. Medicament, characterized in that it comprises a product according to any one of Claims 1 to 23.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/02336

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/06 A61K31/55 //(C07D487/06,243:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 11690 A (JOUVEINAL) 25 April 1996 (1996-04-25) cited in the application claim 1 -----	1,9,16, 24



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 July 1999

Date of mailing of the international search report

20/07/1999

Name and mailing address of the ISA

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Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/02336

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 24 and 25
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Jnal Application No

PCT/EP 99/02336

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9611690 A	25-04-1996	FR 2725719 A	19-04-1996
		AU 703773 B	01-04-1999
		AU 3749495 A	06-05-1996
		BR 9509353 A	30-12-1997
		CA 2200628 A	25-04-1996
		CN 1160352 A	24-09-1997
		CZ 9701114 A	14-01-1998
		EP 0785789 A	30-07-1997
		HU 77411 A	28-04-1998
		JP 10507447 T	21-07-1998
		NO 971687 A	13-06-1997
		PL 319659 A	18-08-1997
		US 5852190 A	22-12-1998

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- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☒ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☒ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
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